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Array Technologies

Principal Investigator: Chase, Thomas
Grant Number: 5Z01NS002265-28
Title: Pathogenesis And Treatment Of Neurodegenerative Disease

Abstract: Unavailable

Principal Investigator: DAWSON, VALINA L.
Grant Number: 5R01NS040809-04
Title: Mechanisms of Ischemic Tolerance

Abstract: The overall goal of this project is to understand the molecular mechanisms of ischemic tolerance in cortical neurons. Neuronal ischemic preconditioning or tolerance is a phenomenon in which brief episodes of ischemia protect against the lethal effects of subsequent periods of prolonged ischemia. The signaling mechanisms leading to preconditioning are poorly understood but have the potential for providing important pharmaceutical targets for the treatment of patients at risk for ischemic injury and possibly the treatment of patients suffering from chronic neurodegenerative diseases such as Parkinson's Disease. Ischemia can be modeled in vitro by oxygen-glucose deprivation (OGD). We have recently discovered that OGD preconditioning induces p2 p21ras (Ras) activation in a NMDA receptor- and NO-dependent manner. OGD preconditioning is dependent on Ras activation of the Raf-Mek-Erk pathway. Our observations indicate that activation of the Ras/Erk cascade by NO is a critical mechanism for the development of OGD tolerance in cortical neurons, which may also play an important role in ischemic preconditioning in vivo. To further our understanding of preconditioning it is essential to identify the transcriptional elements that are activated and the new proteins that are responsible for this remarkable neuroprotection. In this project we propose to investigate the role of transcriptional targets of the Ras/Erk signaling cascade with a focus on CREB and Elk activation. We will identify genes that are regulated by preconditioning and determine which genetic changes are responsible for preconditioning. Preconditioning can also be induced by potassium depolarization in an in vitro model of spreading depression. We will investigate whether similar or different mechanisms are responsible for potassium depolarization induced tolerance. We anticipate that this series of investigations will identify endogenous protective mechanisms that ultimately may be harnessed as novel protective strategies against ischemic and traumatic injury as well as chronic neurodegenerative disorders such as Parkinson's Disease. -

Principal Investigator: GLANZER, JASON G
Grant Number: 5F32NS046894-02
Title: Single-cell expression profiling of primary astrocytes

Abstract: Recent evidence has shown that astrocytes, a subset of glia, are capable of introducing and propagating calcium waves in vitro. Astrocyte processes are in close contact with synapses and can alter synaptic activity through regulation of glutamate in the perisynaptic space. The ability of astrocytes to propagate waves and alter synaptic activity suggest that these cells play active roles in brain signaling. Currently, astrocyte characterization has been based on morphological studies, whereas expression profiling of neurons has resulted in distinct classifications of cells based on the genes they express, which is often related to localization and function within the brain. Astrocyte subtypes may also exist in coordination with their neuronal partners. Therefore, we hypothesize that distinct astrocyte expression subtypes exist in the brain that are important for proper brain signaling and function. Using single-cell RNA amplifcation and DNA-array methods, we intend to develop an expression profile for primary astrocytes from different locations of the brain. Our laboratory has been successful in detecting both active translation and transcript specificity in dendrites. Likewise, we intend to identify the presence of active translation in astrocyte processes and identify what subset of mRNA transcripts are localized to the astrocyte processes. Expression profiling of astrocyte and astrocyte processes will provide a benchmark for future studies in characterizing these cells and may provide insight on pathological conditions thought to involve astrocyte dysfunction, such as multiple sclerosis, Parkinson's disease, and glioma.-

Principal Investigator: KIM, KWANG S
Grant Number: 5R21NS044439-02
Title: DA-specific gene discovery and promoter engineering

Abstract: Gene therapy techniques need substantial development to provide therapeutic possibilities for treating neurological disorders such as Parkinson's disease (PD). Based on molecular control mechanisms of noradrenergic neuron-specific gene regulation, we recently devised a gene delivery system that can efficiently target transgene expression to noradrenergic neurons in a cell-specific manner. Our long-term goal is to establish gene therapy system(s) that will drive efficient transgene expression in a dopamine (DA) neuron-specific fashion based on discovery and characterization of DA-specific genes. Toward this end, we propose to identify and isolate genes that are selectively expressed in the DA mid-brain area by analyzing gene expression profiles using the most comprehensive cDNA microarrays such as the augmented NIA 16K chip and augmented RIKEN 16 K chip. Because these chips do not cover the whole genome yet, we will also identify novel DA-specific genes by the PCR-based subtractive hybridization techniques. Expression patterns of putative DA-specific genes will be tested by semi-quantitative RT-PCR using independently isolated mRNAs, and will be confirmed by in situ hybridization. Among the isolated DA-specific genes, we will first focus on putative DNA-binding transcription factors. The consensus binding sites for these putative transcription factors will be defined and their potential promoter function will be tested by cotransfection assays using cell line systems. On the basis of the mechanism of action of the novel DA-specific transcription factor(s), synthetic promoters will be developed and optimized. The optimized synthetic promoter will be subcloned in front of the reporter lacZ gene in the context of the self-inactivated lenti viral vectors. Cell type-specific expression of the reporter gene will be examined using both in vitro mesencephalic primary neuronal cultures as well as in different rat brain areas following stereotactic injection. At the later stage of this proposal, we will plan to use our developed promoter system(s) to deliver therapeutic genes (e.g., GDNF and Bcl 2) to the DA neurons and will test whether they can efficiently ameliorate behavioral symptoms in animal models of PD. The proposed research will identify and isolate genes that are selectively expressed in the mid-brain DA area on a genome-wide scale and will characterize their transcriptional regulation. Based on these mechanisms, we will devise novel and innovative DA-specific promoter systems and test them using in vitro and in vivo systems. In combination with safe viral vectors, our developed gene delivery systems can be translated clinically into gene therapy approaches for PD and other neurological disorders, in which DA

Principal Investigator: KONRADI, CHRISTINE
Grant Number: 1R01NS048235-01
Title: Levodopa dyskinesia and striatal neuroplasticity

Abstract: Parkinson's disease (PD) is a brain disorder caused by progressive loss of the brain chemical dopamine. Patients with Parkinson's disease are treated with levodopa (L-DOPA), a precursor of dopamine. However, L-DOPA therapy has disabling side effects. Most patients on L-DOPA treatment are eventually afflicted with motor fluctuations and abnormal, involuntary movements known as dyskinesias. L-DOPA-induced dyskinesias can become more disabling than Parkinson's disease itself. In severe cases, neurosurgical lesioning of basal ganglia nuclei such as the thalamus, pallidum or subthalamic nucleus is needed to improve Parkinson's disease and to minimize L-DOPA dosage. The proposal is based on the hypothesis that L-DOPA treatment in Parkinson's disease, and L-DOPA-induced dyskinesia, are accompanied by unique patterns of gene expression in the putamen. By comparing the gene expression patterns of dyskinesia to non-dyskinesia, we may find the critical factors responsible for the development of dyskinesia, or responsible for preventing the development of dyskinesia. Specific therapies could then be devised that could be co-administered with L-DOPA to prevent dyskinesias. We propose to investigate the molecular systems that are altered in L-DOPA-induced dyskinesia, and to find the 'molecular signature' of dyskinesia. We will study gene expression patterns in the post mortem putamen in Parkinson's disease in response to L-DOPA treatment (PD; Specific Aim 1) and in response to L-DOPA-induced dyskinesia (Specific Aim 2), and compare it to a rat model of L-DOPA-induced dyskinesia (Specific Aim 3). The role of five candidate genes for the development of, or compensation for, dyskinesia will then be examined in the rat model (Specific Aim 4). In a gene array experiment we have already collected data from the rat model of dyskinesia and assembled lists of candidate genes from these data. The lists of genes will be cross-referenced with the findings in the human putamen to determine five most likely candidates to be tested in the rat model. Hypothesis testing will be combined with computer programs that can find interesting new, unanticipated patterns of gene regulation, and help to formulate new hypotheses. The post mortem samples provide us with direct access to the human condition, while the animal model provides us with an experimental system that can be tightly controlled and that permits functional analyses and hypothesis-testing. Together they can lead the way toward new treatments for dyskinesia. -

Principal Investigator: LAWRENCE, MATTHEW S
Grant Number: 1R43NS048786-01
Title: Genomic markers of environmental toxins for Parkinsonism

Abstract: Parkinson's disease is a prevalent and devastating neurodegenerative condition of unknown etiology. One prominent hypothesis holds that the selective loss of the nigrostriatal dopaminergic neurons characteristic of the disease results from damage from environmental neurotoxins in genetically vulnerable individuals. Identifying such environmental contributors to Parkinson s pathogenesis represents a significant public health concern. This project aims to identify the in vivo gene expression changes that occur in the primate brain in response to environmental toxins that have been implicated in the production of Parkinson's and compare these changes with the selective neurotoxin, MPTP, and with the limited knowledge of genetic abnormalities in some Parkinson's patients. Because of the unique vulnerabilities of nonhuman primates and humans to dopamine neurotoxic agents, studies in primates are essential to uncover common genetic markers of toxicity and to reveal the potential toxicity of chemicals of unknown liability. The proposed Phase I studies will test the hypotheses that transcriptional changes that accompany and precede dopamine cell death can be identified using high density gene arrays and bioinformatics in the primate nigrostriatal system in vivo following MPTP exposure. Changes in mRNA initiation of regimen of 3 doses of MPTP over 36 hours that has been established to result in Parkinsonism. Expression changes will also be assessed 6 hours after the administration of a single dose. Changes in nigrostriatal dopamine concentrations and tyrosine hydroxylase immunohistochemistry will be assessed at all time points. Additionally neurobehavioral changes will be assessed in the 20-day animals. Together these data will allow a determination of the sequence of transcriptional changes that parallel or precede histological, biochemical and behavioral events, and allow an assessment of transcriptional events related to acute versus chronic toxicity, with confirmation by quantitative RT-PCR. Defining the chronological and dose dependent gene expression changes induced by MPTP may reveal a transcriptional profile that is predictive of nigrostriatal injury from this toxin. Phase II studies will address whether similar gene expression changes and neuronal injury are seen following exposure to environmentally prevalent compounds that are postulated to be risk factors for the development of Parkinson's disease, and to integrate the resulting transcriptional data into a toxicogenornic database and potentially customized microarrays which may be applied to the assessment of compounds for their possible health risk.-

Principal Investigator: Meredith, Gloria
Grant Number: 5R01NS041799-05
Title: Synaptic Proteins, Trophic Factors and Neurodegeneration

Abstract: One of the most fundamental questions related to the progressive nature of neurodegeneration in human disease is how neurons die. Protecting nerve cells against morphological decline and death requires blocking intrinsic factors that inhibit neural repair. In the present proposal, we offer an innovative approach to study those factors that are active in Parkinson's disease (PD) in a new mouse model that shows synaptic loss and irreversible nigrostriatal degeneration. We propose to track changes of a key synaptic protein, a-synuclein, both in its native environment at presynaptic terminals and under neurotoxic conditions, when it becomes insoluble and accumulates. We will further correlate those changes with altered neurotrophic support. We have established an animal protocol by treating C57/bl mice with a combined regimen of 10 doses of probenecid at 250mg/kg and MPTP at 25mg/kg for 5 weeks. These mice show a slow, progressive loss of nigrostriatal dopaminergic function for at least 6 months, that mimics PD, with no signs of recovery. Three weeks after drug treatment, there is a significant reduction in the number of substantia nigra (SN) cells and dramatic changes in the subsynaptic distribution and density of a-synuclein-immunoreactive terminals. These changes could signal the beginning of a chain of events that leads to cell death. In this proposal, we will focus on the progressive deterioration of dopaminergic neurons in the SN and their inputs, and present three specific aims to be addressed through a series of hypotheses. Specifically, we plan to 1) ascertain the origin and neurochemical phenotype of synapses in the SN that contain a-synuclein and to establish whether MPTP + probenecid treatment leads to their degeneration; 2) determine, in the MPTP+P model, the temporal relationships between cell death and a-synuclein-positive synapses, decline in dopamine function and behavior; and 3) ascertain whether changes in a-synuclein expression and production are precipitated by altered neurotrophic support. The overall objective of our research is to understand the relationship between the synaptic protein, a-synuclein, neurotrophic support, especially brain-derived neurotrophic factor (BDNF) and their respective roles in the PD form of neurodegeneration. The findings of this research should shed light on target areas where neuroprotection strategies can be implemented. -

Principal Investigator: MOSLEY, RODNEY L
Grant Number: 1R21NS049264-01
Title: Neuroprotective Vaccination for Parkinson's Disease

Abstract: Microglia inflammation contributes, in significant measure, to the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) during idiopathic Parkinson's disease (PD). Attenuation of such inflammation could attenuate disease. To this end we show that microglial deactivation responses, induced by vaccination, in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) intoxicated mice improves dopaminergic neuronal survival. This was achieved by adoptively transferring spleen cells from copolymer-1 (Cop-1) immunized mice to MPTP-treated recipients. Spleen cells from ovalbumin (OVA) injected mice failed to affect neuronal protection. Thus, our preliminary works show that protection from dopaminergic neurodegeneration can be achieved by adaptive immunity with T cells specific for Cop-1. Based on response kinetics, antigen specificity, and functional adaptive T cell immune responses, we predict that the mechanism(s) of neuroprotective immunity can be realized and could provide novel treatment strategies for human disease. Our hypothesis posits that protection from dopaminergic neurodegeneration by Cop-1 vaccination is generated through immune cell-mediated mechanisms with specificity for Cop-1 peptides and self-antigens. To investigate this we will adoptively transfer T lymphocytes, B cells and monocytes from Cop-1 immunized mice into MPTP-treated animals. Neuroprotection will be assessed by numbers of dopaminergic neurons, neurotransmitter levels, and neuronal metabolites by magnetic resonance spectroscopic imaging (MRSI). Immune cell populations, proven relevant to neuroprotection will be evaluated for the expression of gene products that are cell population specific as candidates for neuroprotection. Genetic fingerprint analysis will include cDNA microarray analysis and proteomics. This approach takes advantage of an integrated and well-established research program within the Center for Neurovirology and Neurodegenerative Disorders and builds upon research activities in PD supported previously through private donations. These approaches could prove useful for treatment of human PD. -

Principal Investigator: PALLANCK, LEO J
Grant Number: 1R21NS048362-01
Title: Mutational Analyses of Drosophila DJ-1 Homologs

Abstract: Parkinson's disease is a prevalent neurodegenerative disorder characterized by tremors, rigidity, and bradykinesia. These symptoms arise from the degeneration of dopaminergic neurons in the substantia nigra. The cellular and molecular mechanisms responsible for neurodegeneration in Parkinson's disease remain poorly understood, although genetic and environmental factors both appear to play contributing roles. Recently, loss-of-function mutations in DJ-1, a gene of unknown function, were found to be responsible for an autosomal recessive form of Parkinson's disease. To explore the normal biological function of DJ-1, and the mechanism by which loss of DJ-1 function results in neurodegeneration, we propose to subject a pair of highly conserved Drosophila DJ-1 homologs (designated DJ-1a and DJ-1b) to mutational analysis. DJ-1a and DJ-1b function will be perturbed using P element mutagenesis, gene-targeting and double stranded RNA interference methods. The phenotypes resulting from perturbation of these genes will be fully characterized, including an analysis of dopaminergic neuron integrity. Additionally, we will characterize the global gene expression changes resulting from loss of DJ-1a and DJ-1b function and initiate screens for genetic modifiers of the DJ-1a and DJ-1b phenotypes to elucidate the biochemical pathways in which these genes function. This work should clarify the normal cellular role of DJ-1 and provide a foundation for further hypothesis-driven investigation of DJ-1 function. -

Principal Investigator: THOMAS, ELIZABETH A
Grant Number: 5R01NS044169-03
Title: Towards Mechanistic Explanations of Striatal Disorders

Abstract: The broad goals of this application are to identify mechanisms associated with the functions of the striatum under normal and pathological conditions. The striatum is the primary region of dysfunction in several neurodegenerative disorders, such as Huntington's and Parkinson's diseases, and is also associated with movement disorders and psychiatric disturbances. Presently, treatment strategies for these disorders are not curative, but rather are aimed at reducing symptoms. Hence, a better understanding of the mechanisms and pathways that contribute to striatal function is essential. The logic that has motivated our studies is that mRNA molecules with restricted expression in the striatum are likely to encode proteins that are preferentially associated with particular physiological processes of this region. In Specific Aim 1, we will identify and isolate all known genes with specific or enriched expression in the striatum using the systematic, automated mRNA display technology TOGA (Total Gene expression Analysis). We will then create a cDNA microarray chip containing all known and newly discovered striatal-enriched species (100). This will provide us with a DNA tool for analyzing the expression status of all striatal-evident genes under various pathological conditions. In this application, we will focus on the pathology of Huntington's disease (HD), (although additional/future studies will investigate other striatum disorders). HD is an inherited, neurodegenerative disorder characterized by progressive motor, psychiatric, and cognitive disturbances. In Specific Aim 2, we will identify genes associated with HD by screening the striatal-enriched DNA chip with RNA from the brains of transgenic HD mice. These mice express exon 1 of the human HD gene carrying an extremely expanded CAG repeat. Finally, we will test the hypothesis that the HD gene product, huntingtin, interacts with proteins that are enriched in the striatum, hence, giving rise to the tissue-specific degenerative patterns observed in this disease. We will screen all striatum-enriched proteins simultaneously for specific interactions with both normal and mutated forms of the huntingtin. This will be achieved by creating a protein microarray chip containing GST-fusion proteins of each striatal-enriched gene and then probing with biotinylated-labeled huntingtin. The molecules identified in these studies could targets for novel therapies that would prevent or slow the onset of symptoms as well as the progression of Huntington's disease, and very well may lead to cures for this and other devastating neurodegenerative disorders. An important advantage of these potential pharmaceutical targets is that they would act only at the restricted site of expression, the striatum. -

Principal Investigator: VANCE, JEFFREY M
Grant Number: 2P50NS039764-06
Title: The Genetics of Parkinsonism

Abstract: This is a continuation application of our very successful Morris K. Udall Parkinson Disease Research Center of Excellence, seeking to identify genes that contribute to risk of developing PD. Four projects and two cores are proposed. Project I, "Candidate genes and complex interactions in PD," continues the association studies of potential susceptibility genes with PD, derived from biological candidates and the gene expression studies of Project II. Additional specific aims are gene-gene and environmental-gene interactions. Project II, "Expression Analysis and Genomic Convergence," continues and extends our expression studies of tissue obtained by our autopsy program by adding examination of the putamen and the anterior olfactory nucleus to the SN, as well as using Laser Capture Microscope to investigate specific cell types. Genes identified in project II will be tested for association in collaboration with Project I. Project III, "Mitochondrial genetics and PD," builds upon our finding of a highly significant association of mitochondrial-encoded proteins with PD, specifically the haplogroups J and K and SNP 10398, which lies in the complex I subunit ND3. Using cybrids, it looks for functional differences associated with these different mitochondrial haplogroups. It also will examine nuclear mitochondrial genes with significant differential expression in Project II for association with PD. Project IV, "Association Mapping in PD Linkage Regions," will identify PD genes in regions of linkage on chromosomes 5, 8, and 9 through a new approach, genomic "iterative" association mapping, using a new DNA pooling strategy. Once the strongest region of association is identified, haplotype-tagging will be utilized to fine map the region further. Genes lying in the region will be tested for association with PD. The projects depend heavily on our productive cores. In Core B we continue our very successful collection of PD patients and siblings, as well as our prospective autopsy program. Core C provides neuropathology support for investigation and diagnoses of autopsy material, brain banking and genotyping support for the projects. We believe that by utilizing these different but integrated approaches and resources we will be able to define the genetic contributions to PD. -

Principal Investigator: VANCE, JEFFREY M
Grant Number: 5R01NS031153-11
Title: Genomic Screen To Identify Alzheimers Disease Genes

Abstract: To identify genes influencing age at onset (AAO) in two common neurodegenerative diseases, we performed a genomic screen for AAO in families with Alzheimer disease (AD;) and Parkinson disease (PD. (Li et al, AJHG, April, 2002). Heritabilities between 40 percent-60 percent were found in both the AD and PD datasets. For PD, significant evidence for linkage to AAO was found on chromosome 1p (LOD =3.41). In addition, evidence for AAO linkage on chromosomes 6 and 10 was identified independently in both the AD and PD data sets. Subsequent unified analyses of these regions identified a single peak on chromosome 10q between D10S 1239 and D10S 1237, with a maximum LOD score of 2.62. These data suggest that a common gene affects AAO in these two common complex neurodegenerative diseases. We propose to further map and identify the genes contributing to this age-of-onset effect. We will continue to collect new AD and PD families to further map the peaks, and test candidate genes within the region for association to age of onset in these two disorders. Candidates will be prioritized using initially obvious biological candidates, then candidates that lie within the linkage peaks that are identified through Serial Analysis of Gene Expression and Microarray studies in both AD and PD (being performed in our lab in concurrent studies) and finally through fine mapping of the linkage peak for high areas of association using a DNA pooling approach and a new Single base pair- denaturing high performance liquid chromatography methodology. Candidates lying within these high association areas will be investigated further. Once identified, the genes will be investigated in collaboration with known mouse models, at present the Parkin model of Dr. Jian Feng and the APOE models of Dr. Don Schmechel of the DUMC Alzheimer Disease Research Center. Identifying age-of-onset genes may lead to treatment and delay of these late-onset disorders and a better understanding of the pathological processes they share.-

Principal Investigator: YOUNG, ANNE B
Grant Number: 2P50NS038372-06A1
Title: MGH/MIT MORRIS UDALL CENTER OF EXCELLENCE IN PD RESEARCH

Abstract: The MGH/MIT Morris Udall Center of Excellence in PD Research is taking a broad, collaborative and interactive approach to the study of Parkinson's disease. The Projects address critical questions concerning the selective vulnerability of dopamine neurons, the mechanism and consequences of Lewy body formation and alpha-synuclein aggregation, the neural systems consequences of parkinsonism and synuclein pathology, and molecular approaches for modifying this pathology. These issues will be explored using a range of systems, from yeast genetics, to mammalian cell culture, to rodent models to human postmortem material. The Center incorporates state-of-the-art technologies including high throughput yeast genetic screens to identify modifiers of synuclein aggregation and toxicity, viral vector gene transfer to study factors in mammalian cell culture and rodent models, multi-unit tetrode recordings to study striatal plasticity, fluorescence lifetime imaging to study protein-protein interactions, and laser capture microdissection and gene arrays to study transcriptional dysregulation. The Center has a Clinical and Training Core that provides care to patients with Parkinson's disease, gathers data on clinical features of the disease and response to therapy, solicits brain donations for neuropathological study, and trains outstanding clinician scientists to be future leaders in the field. The Center also has a Bioinformatics Core that serves to integrate and analyze data across the projects, and facilitate sharing of the information. The Administrative Core is charged with management of the Center and facilitating the sharing of information, ideas, and reagents among the investigators and with other components of the Udall Centers consortium. The investigators of the MGH/MIT Center are dedicated to a program of collaborative and interactive studies which will lead to better treatments for people with Parkinson's disease.-

Principal Investigator: ZIGMOND, MICHAEL J
Grant Number: 3P50NS019608-19A1S1
Title: Neuroprotection and early detection in PD

Abstract: Unavailable

Principal Investigator: ZIGMOND, MICHAEL J
Grant Number: 5P50NS019608-20
Title: Neuroprotection and early detection in PD

Abstract: Parkinson's disease (PD) poses a serious threat to the health of a large segment of our society. This is an extensively revised renewal application for a Program Project Grant now in its 18th year. During much of the history of the PPG, we have focused on the compensatory changes that underlie the preclinical phase of PD. That line of investigation will continue, while at the same time we will also add two new foci: first, the development of neuroprotective strategies and, second, the detection of PD it its preclinical phase. Neuroprotection: This will now provide the principal long-term focus of the entire PPG. Our approach derives from recent evidence from our labs indicating that the contralateral motor neglect and loss of DA normally following unilateral damage to the nigrostriatal DA projection can be ameliorated by forced use of the contralateral limb. We hypothesize that forced execution of a motor act that is otherwise compromised by PD is neuroprotective, and that this results from an interaction between the motor act, injury, and concomitant increase in the availability of one or more trophic. We will explore this hypothesis using our 6-hydroxydopamine (6-OHDA) rat model. Our work will involve studies of the role of trophic factors (e.g., GDNF, BDNF, and FGF2), estrogen, and aging, as well as anatomical studies to differentiate between protection, rescue and sprouting (Project 1: M. Zigmond, PI). We also use multineuron recording in awake animals to examine the effect of forced use on the functioning of the basal ganglia more broadly (Project 2, D. Woodward, PI). Compensation: In the past, our studies of compensation have focused our studies on adaptations within the nigrostriatal dopamine (DA) system. Our multineuron recordings will now allow us to explore adjustments within other components of the basal ganglia (Project 2: D. Woodward, PI). Early detection: For neuroprotective strategies to be most effective, it is likely that they must be applied as early in the course of the disease as possible. In this respect, the compensatory changes noted above represent a problem to be overcome through the development of diagnostic tests that can detect PD before the emergence of gross neurological deficits. To do so we will develop a multi-dimensional clinical test battery, using PET imaging as the ultimate criteria for nigrostriatal damage (Project 3, N. Bohnen, PI). We believe that by combining a variety of basic, translational, and clinical approaches we will make significant progress toward the development of a therapeutic approach to PD.-